ESMO PRECEPTORSHIP ON HNC
Radio(chemo)therapy for head and neck cancer
HNSCC: indications and modalities

Prof Dr Sandra Nuyts
Radiotherapy - Oncology
May 2019
- Nothing to disclose
Half million new cases HNC/year in world

50-60% cured

Less side effects
More organ and function preservation

not cured

local failure

More effective local and systemic treatment

distant failure

More effective systemic treatment
Current standard treatment for early HNC: radiotherapy or surgery

- Surgery (organ sparing)
- Radiotherapy alone
  - Often altered fractionation schedules
Current standard treatment for locally advanced HNC: chemoradiotherapy or surgery

- Inoperable locally advanced HNC: CRT
- Operable locally advanced HNC
  - CRT: Organ and function preservation
  - Surgery + postoperative (C)RT
CANCER TREATMENT

- surgery
- chemotherapy
- hormonal therapy
- immunotherapy
- radiotherapy
Attom level

“Ionizing atoms”

Photon

“Damaging molecular structure of DNA”

Molecular level

Cellular level

“Impacting intra-cellular mechanism”

“Impacting processes in the human body”

Atomic level

Lineal accelerator

Ion

Free electrons
Advances in radiotherapy for HNC

• 1. Lessons from randomized trials

• 2. IMRT: beyond parotid sparing?

• 3. New approaches
Radiotherapy for HNC

- **Primary setting**
  - Chemoradiotherapy
  - Bioradiotherapy
  - Altered fractionation

- **Postoperative setting**
  - Radiotherapy
  - Chemoradiotherapy
Current standard treatment for **locally advanced HNSCC**: chemoradiotherapy

- Inoperable locally advanced HNSCC
- Operable locally advanced HNSCC
  - Organ and function preservation
Concurrent therapy

• At current: 2 options
  – Chemoradiotherapy (CRT): based on data from thousands of patients
  – ‘Bio’radiotherapy (BRT): based on 1 trial
chemoradiotherapy

Pignon, Lancet 2000
Chemoradiotherapy meta-analysis

(a) Hazard ratio

<table>
<thead>
<tr>
<th>Timing</th>
<th>Concomitant</th>
<th>Induction</th>
<th>Adjuvant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concomitant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Induction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adjuvant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterog:  
Test for interact:

(a) Concomitant chemotherapy.

![Graph showing survival analysis](image)

- **Survival (%)**
  - Concomitant chemotherapy
  - Control

- **Absolute difference at 5 years ± standard deviation:** 6.6 ± 1.2%
- **HR [95% CI]**
  - Concomitant chemotherapy: 0.61 [0.57, 0.66]
  - Control: 0.98 [0.90; 1.02]
  - Total: 1.06 [0.95; 1.16]
  - 0.86 [0.85, 0.92]

<table>
<thead>
<tr>
<th>Death/person-years by period</th>
<th>Years 0-2</th>
<th>Years 3-5</th>
<th>Years &gt; 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>2500/6298</td>
<td>672/3658</td>
<td>217/2437</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>2167/6647</td>
<td>706/4576</td>
<td>275/3194</td>
</tr>
</tbody>
</table>

16485 pts  
87 trials  
Pignon et al, R&O 2009
Radiochemotherapy

Pignon, Radiother Oncol 2009

16485 pts
87 trials

Radiotherapy

Concomitant Radiotherapy + Chemotherapy

Local failure
63.2%

Distant failure
49.7%

18.9%
16%

Time from randomisation (Years)
chemoradiotherapy: which chemotherapy?

- Only 2 combinations based on randomised studies:

  - Carbo (70mg/m$^2$)-5FU (600mg/m$^2$ x4d) 3 weekly
    * Calais et al JNCI 1999
  
  - CDDP 100mg/m$^2$ 3 weekly
    * Bernier et al EORTC NEJM 2004
    * Cooper et al RTOG NEJM 2004
    * Forastiere et al Intergroup RTOG91-11 NEJM 2003
CRT results in significant increase in acute toxicity

- Grade 3+: 77% with CRT vs 34% with RT alone (p<0.001)
CRT: late toxicity!

- Analysis of 3 RTOG trials on CRT
- 230 eligible patients: 43% late toxicity

<table>
<thead>
<tr>
<th>Table 3. Types of Late Toxicity Events Seen by Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Feeding tube dependence &gt; 2 years post-radiation therapy</td>
</tr>
<tr>
<td>RTOG late toxicity criteria, grade 3+</td>
</tr>
<tr>
<td>Pharyngeal dysfunction</td>
</tr>
<tr>
<td>Laryngeal dysfunction</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Other (e.g., infection, fistula)</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>No severe late toxicity event (controls)</td>
</tr>
</tbody>
</table>

Abbreviation: RTOG, Radiation Therapy Oncology Group.
*Feeding tube data were not collected at all in RTOG study 91-11.
†Numbers do not always add up along columns, due to some patients having more than one toxicity event.
Newer agents

- molecular targeting: EGFR
  - Overexpression in 80-100% HNC
  - Poor prognostic factor
  - Reduced response to XRT and CT
Phase III studie: Radiotherapy +/- Cetuximab

- Phase III randomised study

Stage III-IV oropharynx, larynx and hypopharynx

Arm 1: XRT (n=213) conventional
BID hyperfractionation concom boost

Arm 2: XRT + weekly Cetuximab (n=211)

NEJM 2006
Lancet Oncol 2010
Results: locoregional control

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>RT+ C225</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration (months)</td>
<td>14.9</td>
<td>24.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Locoregional control rates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>55%</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>2 year</td>
<td>41%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>3 year</td>
<td>34%</td>
<td>47%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Figure 1. Kaplan–Meier Estimates of Locoregional Control among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.

Bonner, NEJM 2006
Results: Survival

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>RT+ C225</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival (months)</td>
<td>29.3</td>
<td>49</td>
<td>0.03</td>
</tr>
<tr>
<td>Survival rates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 year</td>
<td>45%</td>
<td>55%</td>
<td>0.05</td>
</tr>
<tr>
<td>5 year</td>
<td>36%</td>
<td>45.6%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Figure 2. Kaplan–Meier Estimates of Overall Survival among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.
**Toxicity?**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>6</td>
</tr>
<tr>
<td>Acneiform rash</td>
<td>7</td>
</tr>
<tr>
<td>Radiation dermatitis</td>
<td>3</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>5</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>6</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4</td>
</tr>
</tbody>
</table>
Correlation of rash and survival after treatment with EGFR targets

Study:        9923                0141                BOND
Saltz (2001)  2
Saltz (2004)  3
Cunningham    Van Cutsem          Xiong (2004)  4
Kies (2002)  6

Survival (months)

CRC             CRC          CRC            CRC            Pancreatic         SCCHN
No reaction     Grade 2     Grade 1     Grade 2     Grade 3

<table>
<thead>
<tr>
<th>Site of primary tumour</th>
<th>Radiotherapy alone</th>
<th>Radiotherapy plus cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Events</td>
<td>N</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>135</td>
<td>76</td>
</tr>
<tr>
<td>Larynx</td>
<td>51</td>
<td>32</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>27</td>
<td>22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumour stage</th>
<th>Radiotherapy alone</th>
<th>Radiotherapy plus cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJCC T4</td>
<td>65</td>
<td>47</td>
</tr>
<tr>
<td>AJCC T1–3</td>
<td>148</td>
<td>83</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>Radiotherapy alone</th>
<th>Radiotherapy plus cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>122</td>
<td>66</td>
</tr>
<tr>
<td>Other</td>
<td>91</td>
<td>64</td>
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</table>

<table>
<thead>
<tr>
<th>Radiotherapy fractionation</th>
<th>Radiotherapy alone</th>
<th>Radiotherapy plus cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twice daily</td>
<td>37</td>
<td>20</td>
</tr>
<tr>
<td>Once daily</td>
<td>55</td>
<td>35</td>
</tr>
<tr>
<td>Concomitant boost</td>
<td>120</td>
<td>75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall stage</th>
<th>Radiotherapy alone</th>
<th>Radiotherapy plus cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJCC IV</td>
<td>161</td>
<td>101</td>
</tr>
<tr>
<td>AJCC II–III</td>
<td>52</td>
<td>29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nodal stage</th>
<th>Radiotherapy alone</th>
<th>Radiotherapy plus cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJCC N1–3</td>
<td>175</td>
<td>109</td>
</tr>
<tr>
<td>AJCC N0</td>
<td>38</td>
<td>21</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>KPS</th>
<th>Radiotherapy alone</th>
<th>Radiotherapy plus cetuximab</th>
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</thead>
<tbody>
<tr>
<td>90–100</td>
<td>141</td>
<td>76</td>
</tr>
<tr>
<td>60–80</td>
<td>72</td>
<td>54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Radiotherapy alone</th>
<th>Radiotherapy plus cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>169</td>
<td>106</td>
</tr>
<tr>
<td>Female</td>
<td>44</td>
<td>34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EGFR-positive cells</th>
<th>Radiotherapy alone</th>
<th>Radiotherapy plus cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50%</td>
<td>81</td>
<td>50</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>92</td>
<td>57</td>
</tr>
<tr>
<td>Unknown</td>
<td>40</td>
<td>23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Radiotherapy alone</th>
<th>Radiotherapy plus cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥65</td>
<td>65</td>
<td>43</td>
</tr>
<tr>
<td>&lt;65</td>
<td>148</td>
<td>87</td>
</tr>
</tbody>
</table>
RTOG 0522: ACCELERATED RT+ CDDP +/- CETUXIMAB

Ang et al JCO 2014
Take home message 1:

- Golden standard **locally advanced** HNSCC:
  - Radiotherapy + high dose cisplatin
  - If patient not eligible cisplatin: carboplatin-5FU or cetuximab

- What about **early stage** disease?
  - Use of altered fractionation
altered fractionation

- Standard fractionation
- Hyperfractionation scheme
  - Higher total dose
  - Dose/fraction lower
- Accelerated radiotherapy
  - Total treatment shorter
- Combination schedules
RADIOTHERAPY ALONE: ALTERED FRACTIONATION

- Altered fractionation: meta-analyse MARCH group

- All fractionation-schedules: 6.4% gain 5y locoregional co

- Hyperfractionation schedule: gain 9.4%

Bourhis, Lancet 2006 +
update Lacas Lancet Oncol 2017

6515 pts  15 trials
ALTERED FRACTIONATION: META-ANALYSE
MARCH GROUP

• All fractionation schedules: 3.1% gain 5y overall survival
• Hyperfractionation schedules: gain 8.1%

Lacas, Lancet Oncol 2017

33 trials, 11423 patients
## WHICH RADIOTHERAPY REGIMEN?

<table>
<thead>
<tr>
<th></th>
<th>Hyperfractionation</th>
<th>Accelerated fractionation without total dose reduction</th>
<th>Accelerated fractionation with total dose reduction</th>
<th>p*</th>
<th>Overall</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional</td>
<td>0.76 (0.66–0.89)</td>
<td>0.79 (0.72–0.87)</td>
<td>0.90 (0.80–1.02)</td>
<td>0.15</td>
<td>0.82 (0.77–0.88)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Local control</td>
<td><strong>0.75 (0.63–0.89)</strong></td>
<td><strong>0.74 (0.67–0.83)</strong></td>
<td><strong>0.83 (0.71–0.96)</strong></td>
<td>0.50</td>
<td>0.77 (0.73–0.83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Regional control</td>
<td>0.83 (0.66–1.02)</td>
<td>0.90 (0.77–1.04)</td>
<td>0.87 (0.72–1.06)</td>
<td>0.83</td>
<td>0.87 (0.79–0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Metastatic control</td>
<td>1.09 (0.76–1.58)</td>
<td>0.93 (0.74–1.19)</td>
<td>0.95 (0.68–1.32)</td>
<td>0.77</td>
<td>0.97 (0.82–1.15)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

*Comparison of the three hazard ratios for each type of radiotherapy. †Test of overall treatment effect. ‡Data from 14 trials; for three trials, only locoregional failure without specification if the failure was local, regional, or both, was available.

Table: Hazard ratio (95% CI) of altered fractionated radiotherapy versus conventional radiotherapy on overall population and by type of radiotherapy for locoregional, local, regional, and metastatic control (n=7073)

Bourhis, Lancet 2006
<table>
<thead>
<tr>
<th>Autor</th>
<th>Regimen</th>
<th>Gr3-4 mucositis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Contr</td>
</tr>
<tr>
<td>Horiot (n=356)</td>
<td>HF</td>
<td>49%</td>
</tr>
<tr>
<td>Horiot (n=512)</td>
<td>Acc fract + split</td>
<td>50%</td>
</tr>
<tr>
<td>Dische(n=918)</td>
<td>CHART</td>
<td>43%</td>
</tr>
<tr>
<td>Fu (n=536)</td>
<td>Acc fract (conc boost)</td>
<td>25%</td>
</tr>
<tr>
<td>Fu (n=524)</td>
<td>Acc fract + split</td>
<td>25%</td>
</tr>
<tr>
<td>Fu (n=507)</td>
<td>HF</td>
<td>25%</td>
</tr>
<tr>
<td>Skladowski (n=99)</td>
<td>Acc Fract</td>
<td>26%</td>
</tr>
</tbody>
</table>
CONCLUSION ALTERED FRACTIONATION SCHEDULES

• Indications:
  – T2 or T3 tumors or N0-N1 disease (TNM7)
  – More advanced disease and chemo not an option
Take home message 2: 70 Gy in 7 weeks alone = perhaps the worst we can do...!

RT-CT

Altered fractionation

+8-10%

+8%

Induction chemotherapy

+???

Cetuximab+ RT

+10%
WHAT ABOUT INDUCTION CHEMO IN OPC?

• No data to support this: overall survival data

Budach W et al R&O 2016
RADIOTHERAPY + CHEMO: ROLE FRACTIONATION?

XRT
Conventional fractionation

XRT + conc chemo

+8%
GORTEC 99-02 randomized trial

Stage III/IV

- Conventional RT + Carbo/5FU
  - 70Gy 7 weeks +3 chemo

- Accelerated RT + Carbo/5FU
  - 70Gy 6 weeks +2 chemo

- Very accelerated RT
  - 64.8Gy 3.5 weeks

N = 840 pts randomized, 2/3 of oropharynx
Overall survival

GORTEC-9902 - Progression free survival

At risk

<table>
<thead>
<tr>
<th></th>
<th>279</th>
<th>162</th>
<th>102</th>
<th>64</th>
<th>45</th>
<th>29</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>280</td>
<td>151</td>
<td>99</td>
<td>70</td>
<td>64</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>281</td>
<td>129</td>
<td>81</td>
<td>64</td>
<td>47</td>
<td>31</td>
</tr>
</tbody>
</table>

Overall survival

Median FU: 5.2 y

Bourhis et al Lancet Oncol 2012
RTOG 0129

- phase III trial, stage III-IV HNC accelerated concomitant boost (AFX-C, 72 Gy/6 W) + 2x cisplatin (CDDP) versus standard fractionation (SFX, 70 Gy/7 W) + 3x cisplatin (CDDP)

70Gy in 6 weeks + 2x CDDP = 70 Gy in 7 weeks + 3x CDDP

Nguyen-Tan et al JCO 2014
FOLLOW UP OF THE NECK? PET-NECK TRIAL

Mehanna H et al NEJM 2016

- 564 patients (84% OPC)
- Randomized surveillance vs planned surgery
- 2y OS 3% better in surveillance group (84,9% vs 81,5%)
postoperative XRT

– Reduces locoregional recurrence rates by at least factor 2
  • Cohort studies
  • Small randomized trials

– Reduced locoregional control translates in survival benefit
SEER database 1539 patients

5y OS T1-2N1 OC with/without postop RT p<0.001 at 60 months

Shrime et al Arch Otolaryngol Head Neck Surg. 2010
Oral cavity: timing PORT

In general: within 6 weeks postop

### Table 1: Overview of studies regarding the prognostic significance of the interval between surgery and radiotherapy.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Interval surgery and radiotherapy</th>
<th>Number of patients</th>
<th>Results</th>
<th>Survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Local-regional control</td>
<td></td>
<td></td>
<td>OS</td>
<td></td>
</tr>
<tr>
<td>Ang (2001)</td>
<td>Retrospective analysis in data from a prospective phase III study</td>
<td>Interval: 0-31 days PORT (63 Gy)</td>
<td>75</td>
<td>5 yr LRC: 80%, 72% *</td>
<td>5 yr OS: 61%, 47% *</td>
<td>No randomization for interval between surgery and radiotherapy</td>
</tr>
<tr>
<td>Basit 2001</td>
<td>Retrospective Multivariate</td>
<td>Interval: &gt; 30 days PORT (46-74 Gy)</td>
<td>201</td>
<td>5 yr LRC: 78%</td>
<td>5 yr OS: 35%</td>
<td>Multivariate analysis: no effect</td>
</tr>
<tr>
<td>Muriel 2001</td>
<td>Retrospective Multivariate</td>
<td>Interval: &gt; 50 days PORT (50-76 Gy)</td>
<td>Total: 214</td>
<td>5 yr LRC: 83%</td>
<td>5 yr OS: 28%</td>
<td>Interval independent prognostic factor for LRC</td>
</tr>
<tr>
<td>Parsons 1997</td>
<td>Retrospective Univariate</td>
<td>Interval: &gt; 50 days PORT (55-73 Gy)</td>
<td>39</td>
<td>LRC: 79%</td>
<td>LRC: 56%</td>
<td>Not taken into account in the multivariate analysis</td>
</tr>
<tr>
<td>Peters 1992</td>
<td>Retrospective analysis in data from a prospective phase III study</td>
<td>Interval: &gt; 6 weeks PORT (54-68 Gy)</td>
<td>37</td>
<td>2 yr LRC: 77%</td>
<td>2 yr LRC: 64%</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Schiff 1990</td>
<td>Retrospective Univariate</td>
<td>Interval: &gt; 6 weeks PORT (52-76 Gy)</td>
<td>61</td>
<td>5 yr LRC: 88%</td>
<td>5 yr LRC: 73%</td>
<td>Not mentioned</td>
</tr>
</tbody>
</table>

LRC = local-regional control, OS = overall survival, PORT = postoperative radiotherapy
* Results en p-values for overall treatment time of 3 weeks and 7 weeks, respectively.

5-20% benefit
7-27% benefit S
postop XRT vs preop XRT?

- **RTOG 73-03**: LAHNCC: supraglottic larynx, hypopharynx, oral cavity, oropharynx
- Preop (50Gy) versus postop (60Gy)
  - OC/OP also had definitive RT arm (65-70Gy) followed by surgery if residual disease
- 277 patients, 10 yr follow up
  - Improved LRC in postop arm (65%) vs preop (48%, P=0,04)
  - Trend toward improved survival: 38 vs 33% (p=0,1)
  - Surgical and RT complications ‘similar’
- **RTOG 73-03** established 60Gy as postop RT dose

Tupchong et al, IJROBP 1991;20:21-28
radiation dose based on risk

- MDAnderson prospective randomized trial 240 pts resected stage III/IV OC, OP, HP, L

Peters L et al IJROBP 1993;26:3-11
### ORAL CAVITY: RADIATION DOSE

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Number patients</th>
<th>Actuarial control rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 yr</td>
<td>5 yr</td>
</tr>
<tr>
<td>&lt;= 54</td>
<td>17</td>
<td>63</td>
</tr>
<tr>
<td>57,6</td>
<td>66</td>
<td>92</td>
</tr>
<tr>
<td>63</td>
<td>51</td>
<td>89</td>
</tr>
<tr>
<td>68,4</td>
<td>54</td>
<td>81</td>
</tr>
</tbody>
</table>

Peters et al IJROBP 1993
Rosenthal et al IJROBP 2007
radiation dose based on risk

Risk factors:
- > 1 nodal group
- >= 2 nodes
- Nodes >3cm
- Microscopic + margins
- PNI+
- OC
- ECE

-Low risk: no features
-Intermediate risk: 1 risk factor (no ECE)
-High risk: ECE or >= 2 risk factors

Ang et al IJROBP 2001; 51:571-578
5 yr LRC and OS:
Low risk: 90% and 83%
Intermediate risk: 94% and 66%
High risk: 68% and 42%

Ang et al IJROBP 2001; 51:571-578
Indication PORT

Risk features:

- Microscopically positive surgical margins
- ECE
- LVI
- PNI
- Close margins (0.01-5mm)
- \( \geq 2 \) involved neck nodes
- \( >1 \) positive nodal group
- Oral cavity primary site
- Nodal diameter \( >3 \)cm
- \( >6 \) week interval between surgery and XRT
- Advanced T stage
- Recurrent disease
- Tumor spillage
- Multicentricity
- Invasion of bone/cartilage/skin or soft tissue of the neck
- Depth of tumor invasion
  - \( >3 \)mm (An 2008), \( >4 \)mm (Fakih 1989, O’Brien 2003), \( >5 \)mm (Fukano 1997)
    - (Tumors 3-9 mm: 44% node+, 7% local recurrence; \( >9 \) mm: 53% subclinical node+, 24% local recurrence Head Neck 2002: 24:513-20)
Postoperative RT: role chemo?

– 2 important studies NEJM 2004 high risk group:

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Year reported</th>
<th>No of patients</th>
<th>Primary treatment</th>
<th>Adjuvant therapy</th>
<th>Toxicities – grades 3 and 4</th>
<th>Higher local control rate</th>
<th>Survival difference in favour of ChemoRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC² 22931 (Bernier et al, 2004)</td>
<td>167 with high-risk features</td>
<td>Surgery</td>
<td>ChemoRT (P) RT⁵</td>
<td>Acute: 11 vs 21% Chronic: no difference</td>
<td>Yes 82 vs 69% (at 5 years)</td>
<td></td>
<td>OS: Yes, HR = 0.7, P = 0.02 DFS: Yes, HR = 0.75, P = 0.04</td>
</tr>
<tr>
<td>RTOG³ 9501 (Cooper et al, 2004)</td>
<td>459 with high-risk features</td>
<td>Surgery</td>
<td>ChemoRT (P) RT⁵</td>
<td>Acute: 77 vs 34% Chronic: no difference</td>
<td>Yes 82 vs 72% (at 2 years)</td>
<td></td>
<td>OS: No, HR = 0.84, P = 0.19 DFS: Yes, HR = 0.78, P = 0.04</td>
</tr>
</tbody>
</table>
EORTC 22931:
Treatment Scheme

Primary surgery

Randomise

Post-op XRT
60-66 Gy / 33 f / 6-6.5 wks

Post-op XRT
60-66 Gy / 33 f / 6-6.5 wks
DDP 100 mg/m² d 1, 22, 43
Overall survival

![Graphs showing overall survival for EORTC 22931 and RTOG 9501 trials.](image-url)
Combined EORTC/RTOG analysis

EORTC versus RTOG Eligibility

- Stage III-IV
- OP, OC with level 4 or 5 LN
- Perineural Disease
- Vascular Embolisms

EORTC

Margins +
ECE

2+ pos. nodes

RTOG

Bernier, Cooper Head Neck 2005;27:843
OS for patients WITH positive margin and/or ECE
OS for patients **WITHOUT** positive margin and/or ECE

![Graphs showing survival rates for EORTC 22931 and RTOG 9501 trials.](image)

- EORTC 22931: CRT vs RT, $P = 0.33$
- RTOG 9501: CRT vs RT, $P = 0.78$
Postoperative RT: role chemo?

- Differences in selection criteria explain variation in impact of chemo
- 26-27% of population had OC primaries
- Adjuvant chemo is indicated in
  - Positive margins
  - +ECE

CDDP 100mg/m² 3 weekly!

Head Neck 2005; 27: 843-850
POSTOPERATIVE RT: ROLE CHEMO?

Words of caution:

- increase acute toxicity: doubling acute mucositis gr III/IV (21% vs 41%)
- 3 toxic deaths in study
- only 61% pts received 3 cycles chemo
- EORTC no pts > 70j, in RTOG trial only 5% of pts > 70j
- no reduction in distant metastasis in both trials

- DFS for pts with ECE and/or positive margins still remains poor:
  - 35.7% at 5 yrs (meta-analysis of EORTC and RTOG trial)
Take home message 3: Risk Adaptive PORT depending on pathology

<table>
<thead>
<tr>
<th>Risk Features</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>No radiation</td>
</tr>
<tr>
<td>Intermediate risk (neg margin, no ECE)</td>
<td>Radiation alone to 60Gy</td>
</tr>
<tr>
<td>High risk (pos margin, and/or ECE)</td>
<td>Radiation to 60-66Gy with concurrent cisplatin</td>
</tr>
</tbody>
</table>
Advances in radiotherapy for HNC

1. Lessons from randomized trials

2. IMRT: beyond parotid sparing?

3. New approaches
‘old school’
current
Evolution in RT techniques

2D-RT  1990

3D-RT  2000

IMRT  2010

Arc
Xerostomia is/was one of the most common complications of RT for HNC.

Dirix P., Nuyts S. Cancer 2006
Head and Neck Cancer: IMRT is golden standard

Phase III Multi-Centre Randomised Controlled Trial of Intensity Modulated vs Conventional Radiotherapy in Head and Neck Cancer: PARSPORT

Conventional radiotherapy parallel opposed fields

IMRT sparing left parotid

C. Nutting, et al
Lancet Oncology  febr 2011
Gain with IMRT

RTOG Subjective Salivary Gland toxicity ≥G2

<table>
<thead>
<tr>
<th>Months post treatment</th>
<th>Percentage ≥G2</th>
<th>CRT</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>78</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>47</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>18</td>
<td>20</td>
<td>21</td>
<td>19</td>
</tr>
</tbody>
</table>

*Moderate or complete dryness of mouth poor or no response on stimulation

Loco-Regional Progression Free Survival (LRPFS)

1 year LRPFS (95% CI):
- CRT (n=47): 88.0% (73.5 - 94.8)
- IMRT (n=47): 87.3% (73.9 - 94.1)

Hazard Ratio (IMRT:CRT) = 1.59 (0.67 to 3.80)

Nutting et al. Lancet Oncol 2011
The PARSPORT trial
Reduction dysphagia

superior pharyngeal constrictor muscle
middle pcm
inferior pcm
upper esophageal sphincter
esophagus
base of tongue
supraglottic larynx
glottic larynx

Evolution in RT techniques

2D-RT  3D-RT  IMRT  Arc

Standard IMRT aiming at sparing parotid glands
(PCM $D_{mean} = 60$ Gy)

Swallowing sparing IMRT aiming at sparing parotid glands and superior PCM
(PCM $D_{mean} = 50$ Gy)
Intensity modulated arc therapy (VMAT)
Radiotherapy for head and neck cancer: past-present-future

- 2D-RT: Anno 1970
- 3D-CRT: Anno 1990
- IMRT: Anno 2000
- Proton: Anno 2020
Take home message 4:

• Current radiotherapy techniques offer possibilities to spare critical organs
  – Like parotids, swallowing structures

• To reduce **acute and long term toxicity**

• Quality of radiotherapy is becoming more crucial!
Complexity RT increases

“We are at increased risk of missing very precisely”
(J. Rosenman)
val of

Andrè Fortin,

Vincent Qian Wu,

Wuthrick E et al JCO 2014
• 6212 treated patients 2000-2009
• IMRT treated pats: increased survival if treated by ‘higher volume radiation oncologists’
• For each 5 patients more treated per year: 21 % reduction in all cause mortality
Advances in radiotherapy for HNC

1. Lessons from randomized trials
2. IMRT: beyond parotid sparing?
3. New approaches
Increase dose to ‘parts’ of the tumor: **Dose-painting** on the biological target volume (BTV)

Adaptive (Biological) Image-guided Radiotherapy

**Treatment planning**

**Treatment delivery**

**Correction:**
- Patient positioning
- Anatomy changes
- Biology changes

**Planning biology**

**Treatment biology**

Linac-integrated kV Cone-beam CT
**Immunotherapy: PD-1/PD-L1 inhibitors**

Activated T cell

Inhibitors of PD-1 and PD-L1 prevent the tumour cell from binding to PD-1, enabling the T cell to remain active.
Robert R. Wilson (1914-2000)

“1946: good things can come from the tragedy of war”
The Value of Protons

Protons are physically superior to X-rays:

X-Rays do not stop Continue to travel into normal tissues beyond the target

Penetration Depth (cm)

Dose

X-ray Radiotherapy

PROTONS

Bragg-peak ➔ Protons 🔴 STOP

TUMOR
Proton vs. photon therapy

H&N case

Medulloblastoma case
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Disease sub-site</th>
<th>Methodology</th>
<th>Toxicity evaluated</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romesser et al (2016)</td>
<td>18 proton beam therapy, 23 intensity modulated radiotherapy</td>
<td>Unilateral head and neck cancer (major salivary gland or cutaneous primary)</td>
<td>Retrospective cohort comparison</td>
<td>Mucositis, grade 2 or worse; nausea, grade 1 or worse; dysgeusia, grade 1 or worse; fatigue, grade 1 or worse; dermatitis, grade 2 or worse</td>
<td>52%; 70%; 83%; 91%; 74%; photon 17%; 17%; 22%; 39%; 100%</td>
</tr>
<tr>
<td>McDonald et al (2016)</td>
<td>14 proton beam therapy, 12 intensity modulated radiotherapy, 14 proton beam therapy to primary site and intensity modulated radiotherapy to neck</td>
<td>Nasopharyngeal cancer</td>
<td>Retrospective cohort comparison</td>
<td>Gastrostomy tube dependent at completion of radiotherapy; gastrostomy tube dependent 1 month after radiotherapy; equivalent morphine dose greater than baseline at end of radiotherapy</td>
<td>0.03 (&lt;0.01-0.15)<em>; 0.11 (&lt;0.01-0.61)</em>; 0.09 (0.01-0.57)*</td>
</tr>
<tr>
<td>Sio et al (2016)</td>
<td>35 intensity modulated proton therapy, 46 intensity modulated radiotherapy</td>
<td>Oropharyngeal cancer</td>
<td>Retrospective cohort comparison</td>
<td>Subacute food taste symptoms†; subacute appetite symptoms†; chronic appetite symptoms; subacute mucous symptoms (% with moderate-severe symptoms)</td>
<td>7.7%; 6.37%; 4.14%; 84%; 5.76%; 4.68%; 2.12%; 62%</td>
</tr>
<tr>
<td>Blanchard et al (2016)</td>
<td>50 intensity modulated proton therapy, 100 intensity modulated radiotherapy</td>
<td>Oropharyngeal cancer</td>
<td>Retrospective case-matched control comparison</td>
<td>Patient-rated xerostomia, grade 2-3, 3 months after radiotherapy; gastrostomy tube presence or weight loss &gt;20%, 1 year after radiotherapy</td>
<td>61%; 42%; 25%; 8%</td>
</tr>
<tr>
<td>Holliday et al (2015)</td>
<td>10 intensity modulated proton therapy, 20 intensity modulated radiotherapy</td>
<td>Nasopharyngeal cancer</td>
<td>Retrospective case-matched control comparison</td>
<td>Gastrostomy tube needed during or after treatment</td>
<td>65%; 20%</td>
</tr>
<tr>
<td>Patel et al (2014)</td>
<td>286 charged particle (proton, carbon ion, helium ion, or other), 1186 photon (41 studies included)</td>
<td>Nasal cavity and paranasal sinus cancer</td>
<td>Systematic review and meta-analysis</td>
<td>Neurological toxicity (95% CI)</td>
<td>0.04 (0.02-0.08); 0.20 (0.13-0.31)</td>
</tr>
</tbody>
</table>

MDASI-HN=MD Anderson Symptom Inventory-Head and Neck. * Proton vs photon odds ratio (95% CI). † mean MDASI-HN score.

Table 1: Direct comparisons of photon versus proton toxicity in head and neck cancer

Leeman et al Lancet Oncol 2014
## Ongoing studies

<table>
<thead>
<tr>
<th>Institution</th>
<th>Inclusion</th>
<th>Treatment</th>
<th>Primary endpoints</th>
<th>Study start</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSKCC</td>
<td>Unilateral head and neck targets (salivary, skin tumours)</td>
<td>Randomised to proton beam therapy vs intensity modulated radiotherapy</td>
<td>Acute toxicity</td>
<td>October, 2016</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>Resected esophageal tumours by TORS</td>
<td>Partially sparing proton beam therapy</td>
<td>Local control at 2 years</td>
<td>March, 2016</td>
</tr>
<tr>
<td>MDACC</td>
<td>Stage 1-3 previously untreated oropharyngal squamous cell carcinoma</td>
<td>Intensity modulated proton therapy or transoral surgery</td>
<td>Functional outcome measured with patient-reported outcomes and longitudinal digital wristband activity monitoring of study participants</td>
<td>January, 2015</td>
</tr>
<tr>
<td>Technische Universität Dresden</td>
<td>Previously irradiated head and neck cancer</td>
<td>Proton beam therapy</td>
<td>Late toxicity (24 months after therapy)</td>
<td>July, 2015</td>
</tr>
<tr>
<td>MDACC, NCI, NIDCR</td>
<td>Stage 3-4 squamous cell carcinoma of the oropharynx</td>
<td>Randomised to intensity modulated radiotherapy vs intensity modulated proton therapy</td>
<td>Incidence of severe late toxicity 90 days to 2 years after RT</td>
<td>August, 2013</td>
</tr>
<tr>
<td>MGH, MDACC, NCI</td>
<td>Sarcoma of the spine, sacrum, or base of skull</td>
<td>Intensity modulated proton therapy</td>
<td>Local control at 3 years</td>
<td>December, 2012</td>
</tr>
<tr>
<td>MGH, NIH, NCI, Mayo Clinic</td>
<td>Locally advanced sinonasal tumours</td>
<td>Proton beam therapy or intensity modulated radiotherapy</td>
<td>Local control at 2 years</td>
<td>July, 2011</td>
</tr>
<tr>
<td>MGH, NCI</td>
<td>Brain, head and neck, and skull base tumours</td>
<td>Proton beam therapy</td>
<td>Effectiveness of in-room PET</td>
<td>October, 2010</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>Multiple tumour sites, including head and neck</td>
<td>Proton beam therapy</td>
<td>Number of adverse events at 6-6 weeks</td>
<td>September, 2010</td>
</tr>
<tr>
<td>University of Florida</td>
<td>Carcinoma of the skin of the head and neck with perineural invasion</td>
<td>Combined intensity modulated radiotherapy/proton beam therapy</td>
<td>Grade 3 or higher xerostomia at 1 year</td>
<td>September, 2008</td>
</tr>
<tr>
<td>MGH, DFCL, BWH</td>
<td>Squamous cell carcinoma of the nasopharynx: non metastatic, T2a and/or N0</td>
<td>Proton beam therapy</td>
<td>Acute toxicity, treatment compliance, quality-of-life measures</td>
<td>October, 2006</td>
</tr>
<tr>
<td>MDACC</td>
<td>Skull base chondroma</td>
<td>Proton beam therapy</td>
<td>Time to local recurrence</td>
<td>September, 2006</td>
</tr>
<tr>
<td>University of Florida</td>
<td>Cancer of the nasal cavity and/or paranasal sinuses</td>
<td>Proton beam therapy</td>
<td>Incidence of grade 3 or worse xerostomia at 1 year</td>
<td>August, 2006</td>
</tr>
<tr>
<td>MDACC</td>
<td>Skull base chondrosarcoma</td>
<td>Proton beam therapy</td>
<td>Time to local recurrence</td>
<td>April, 2006</td>
</tr>
<tr>
<td>MSKCC</td>
<td>Cancer of the nasal cavity and/or paranasal sinuses</td>
<td>Endoscopic surgical resection and proton beam therapy</td>
<td>Local control at 2 years</td>
<td>Planned 2012 start</td>
</tr>
<tr>
<td>MSKCC</td>
<td>Recurrent or second primary head and neck cancer, previously treated with radiation</td>
<td>Proton beam therapy</td>
<td>Locoregional control</td>
<td>Planned 2012 start</td>
</tr>
</tbody>
</table>

MSKCC = Memorial Sloan Kettering Cancer Center; MDACC = MD Anderson Cancer Center; MGH = Massachusetts General Hospital; NCI = National Cancer Institute; NIDCR = National Institute of Dental and Craniofacial Research; PET = Positron emission tomography; DFCL = Dana-Farber Cancer Institute; BWH = Brigham and Women’s Hospital; TORS = transoral robotic surgery.

Table 2: Ongoing and planned prospective clinical trials evaluating proton beam therapy for head and neck cancer.
Conclusion:

Radiotherapy for HNC: Enormous progress made